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ORIGINAL ARTICLE

Efficacy of Valsartan versus enalapril in lowering Proteinuria in patients with diabetic nephropathy.

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ABSTRACT… Objective: To compare the effectiveness of valsartan and enalapril in reducing proteinuria in diabetic nephropathy patients. **Study Design:** Randomized Controlled Trial. **Setting:** Medical Floor, Allied Hospital. **Period:** January 3, 2024, to January 9, 2024 (Six Months). **Methods:** The study involved patients enrolled after approval from the Institutional Ethical Review Committee at Punjab Medical College, Faisalabad. Participants were randomly divided into two groups: Group A received valsartan 80mg daily, and Group B received enalapril 10mg daily for 3 months. Patients were monitored for efficacy after 3 months. **Results:** This study show no significant difference between the efficacy of the two drugs, but validation through multicenter studies is needed. **Conclusion:** We concluded that the efficacy of valsartan and enalapril in lowering proteinuria in patients with diabetic nephropathy is equal, and no significant difference is found; however, our results require validation through other multicentre studies.

Key words: Diabetic Nephropathy, Enalapril, Efficacy, Proteinuria, Valsartan.

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INTRODUCTION

Macroalbuminuria, or excretion of more than 300 mg of albumin in a 24-hour collection, or macroalbuminuria coupled with abnormal renal function, as indicated by an abnormality in serum creatinine, calculated creatinine clearance, or glomerular filtration rate (GFR), are the usual criteria used to diagnose diabetic nephropathy (DN). A steady rise in proteinuria, a decline in GFR, hypertension, and a high risk of cardiovascular morbidity and death are the hallmarks of diabetic nephropathy. More than 44% of new occurrences of kidney failure are caused by diabetes, making it the most prevalent cause. Chronic hyperglycaemia is a major risk factor for the development of diabetic nephropathy.[1,2]

The glomerular basement membrane thickening and matrix material buildup in the mesangium are the pathological first alterations that occur concurrently with the development of microalbuminuria. Nodular deposits are then typical, and as high proteinuria develops, glomerulosclerosis gets worse until glomeruli are gradually destroyed and renal function declines. Usually, it develops gradually over the years.[3]

Diabetic nephropathy is the most common cause of ESKD and is a serious complication that affects approximately One-fourth of American adults who have diabetes.[4] ACE inhibitors have been shown in certain trials to have a specialized function in lowering intraglomerular pressure in addition to lowering systemic hypertension. In patients with normotensive diabetes, an ACE inhibitor slows the growth of proteinuria and stops the albumin excretion rate from rising. Improved glycaemic management, strict blood pressure control, and the administration of an ACE inhibitor or ARB are interventions that are effective in reducing the progression of albuminuria.[5]

Enalapril and losartan alone were found to reduce proteinuria by 33% in the literature ($p < 0.05$).[6] Another study shows the mean percentage reduction in proteinuria was 25.68 ± 21.40 with enalapril.[7] while the mean percentage reduction in proteinuria with valsartan is 33% (27-38%) (33 ± 21.4).[8]

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Some studies show that enalapril and valsartan have equal efficacy in reducing proteinuria, i.e., 33%.[7,9] Others, however, demonstrate that enalapril is less effective, with a reduction of only 25%. The rationale for my study is that if recent studies indicate that valsartan is more effective in our population, which is genetically and geographically different from other populations, then future recommendations could favour using valsartan, as it may be more cost-effective and avoid side effects like a dry cough.

OPERATIONAL DEFINITION

Efficacy

- Diabetic nephropathy was diagnosed by ACR (Albumin to creatinine ratio) >20mg/mmol.
- Efficacy was measured by monitoring ACR at 3 months.

The drug was considered effective if the ACR became less than 10 mg/mmol

HYPOTHESIS

Null Hypothesis

Two medications are equally effective at reducing proteinuria in diabetic nephropathy patients.

Alternative Hypothesis:

- There is a difference in the efficacies of two drugs

METHODS

This randomised controlled trial was conducted at Medical OPD, Allied Hospital, Faisalabad from January 3, 2024, to January 9, 2024 (six months) following ERC clearance, vide letter No. 48.ERC/FMU/2023-24/412, Dated: 06/08/24.

The WHO sample size calculator for two means was used to determine the sample size. The population mean test value was 33.[7] The population was expected to be 25.68[9] The pooled standard deviation is 21.4%. The study power was 80%. Level of significance 5%. Sample size was 204 (102 in each group).

The Sampling Technique used was Non-probability consecutive sampling.

Inclusion Criteria

- Patients of both genders aged 35-70yr years old
- Fasting blood sugar >126mg dl or on treatment for diabetes
- Patients with BP >= 120/80

Exclusion Criteria

1. Patients having Diabetes Mellitus Type I.
2. Patients having nephropathy due to
   a. bladder outlet obstruction
   b. Interstitial nephritis
   c. chronic glomerulonephritis
3. Patients with UTI, i.e., pus cells >10/HPF, confirmed on medical record

Data Collection Procedure

Following institutional ethical review board permission, the study was done in Faisalabad Medical University, screening of the participants with pre-decided criteria, and consent was taken from each participant. In the study. All the participants were randomly divided into two groups. Group A was given valsartan 80mg single dose daily, & group B was given enalapril 10mg as a single dose daily using computer computer-generated random number table for 3 months. 1st dose of the drug was supervised, and BP was checked after 1 hour to avoid 1st dose hypotension. Patients were followed after 3 months for efficacy by monitoring albuminuria as mentioned in the operational definition. All the information was recorded on a pre-designed form by the researcher.

Data Analysis

Version 20 of SPSS software was utilized for data entry and analysis. For quantitative data such as age, blood glucose levels, ACR, and the length of diabetes, the mean and standard deviation were computed. Gender and efficacy were examples of qualitative variables for which frequency and percentage were computed. To use According to the chi-square test, $p < 0.05$ was considered significant. Stratification was used to control for variables such as age, gender, and length of diabetes. The post-stratification chi-square test was used to determine that a p-value (< 0.05).

RESULTS

To assess the effectiveness of valsartan versus enalapril in reducing proteinuria in patients with diabetic nephropathy, 204 participants (102 in each

group) who met the selection criteria were included.

In Group-A, 42.16% (n=43) and Group-B, 45.10% (n=46), were between the ages of 35 and 50, while Group-A's 57.84% (n=59) and Group-B's 54.90% (n=56) were between the ages of 51 and 70. Group A's mean+sd was 51.06+8.42 years, whereas Group B's was 50.73+8.06 years. (Table-I)

The gender distribution shows that 31.37% (n=32) of Group-A and 35.29% (n=36) of Group-B were female, while 68.63% (n=70) of Group-A and 64.71% (n=66) of Group-B were male. (Table-II)

In Group A, the mean duration of diabetes was 6.57+2.99 years, while in Group B, it was 6.52+3.01 years. (Table-III)

Mean blood glucose levels in Group A were 139.31+7.69 and 141.20+7.42 in Group B. (Table-IV)

Mean ACR levels in Group A were 24.72+2.19 and 24.57+2.04 in Group B. (Table-V)

Comparison of efficacy of valsartan vs enalapril in lowering proteinuria in patients with diabetic nephropathy" shows that in Group-A, 37.25% (n=38) and 28.43% (n=29) in Group-B, while 62.75% (n=64) in Group-A and 71.57% (n=73) in Group-B had no efficacy, p value was 0.17. (Table-VI)

Stratification was used to adjust for variables such as age, gender, and length of diabetes. To apply the post-stratification chi-square test, $p < 0.05$ was considered significant. (Table-VII)

TABLE-I

Distribution of age (n=204)

Age (in years)	Group-A (n=102)		Group-B (n=102)	
	No. of Patients	%	No. of Patients	%
35-50	43	42.16	46	45.10
51-70	59	57.84	56	54.90
Total	102	100	102	100
Mean+SD	51.06+8.42		50.73+8.06	

TABLE-II

Distribution of gender (n=204)

Gender	Group-A (n=102)		Group-B (n=102)	
	No. of patients	%	No. of patients	%
Male	70	68.63	66	64.71
Female	32	31.37	36	35.29
Total	102	100	102	100

TABLE-III

Mean duration of diabetes (n=204)

Duration of Diabetes (Years)	Group-A (n=102)		Group-B (n=102)	
	Mean	SD	Mean	SD
	6.57	2.99	6.52	3.01

TABLE-IV

Mean blood glucose levels (n=204)

Blood Glucose Levels	Group-A (n=102)		Group-B (n=102)	
	Mean	SD	Mean	SD
	139.31	7.69	141.20	7.42

TABLE-V

Mean ACR (n=204)

ACR Levels	Group-A (n=102)		Group-B (n=102)	
	Mean	SD	Mean	SD
	24.72	2.19	24.57	2.04

TABLE-VI

Comparison of efficacy of Valsartan Vs Enalapril in lowering proteinuria in patients with diabetic nephropathy" (n=204)

Efficacy	Group-A (n=102)		Group-B (n=102)	
	No. of Patients	%	No. of Patients	%
Yes	38	37.25	29	28.43
No	64	62.75	73	71.57
Total	102	100	102	100

P value: 0.17

TABLE-VII

Stratification of efficacy with respect to age, gender, and duration of diabetes. (n=204)

Parameter/ Group (n=204)	Efficacy		P-Value
Age 35-50 years	**Yes**	**No**	
A	19	24	0.006
B	8	38	
Age 51-70 years			
A	19	40	.55
B	21	35	
Gender			
Male			
A	29	41	0.17
B	20	46	
Female			
A	9	23	
B	9	102	
Duration of Diabetes			
5 YEARS			
A	16	23	0.06
B	9	32	
➢ **5 Years**			
A	12	3	0.02
B	20	41	

DISCUSSION

DM-II raises the risk of renal and cardiovascular conditions when micro-albuminuria develops. among many parts of the world, the prevalence of end-stage renal disease among people with DM-II has increased. There is mounting evidence that one of the main therapy objectives for renal and perhaps cardiovascular protection is the reduction and normalization of proteinuria. ACE inhibitors have been shown in certain trials to have a specialized function in lowering intraglomerular pressure in addition to lowering systemic hypertension. In patients with normotensive diabetes, an ACE inhibitor slows the growth of proteinuria and stops the albumin excretion rate from rising. Improved glycaemic management, perfect blood pressure control, and the administration of an ACE inhibitor or ARB are interventions that are effective in reducing the course of albuminuria.

Some of the studies reveal equal efficacy of enalapril and valsartan in reducing proteinuria, i.e, 33%.[10,11] While others show comparatively less efficacy of enalapril in reducing proteinuria, i.e, 25%[12] The rationale of my study is that if recent studies showed more efficacy of valsartan in our population, which is genetically and geographically different from other populations, then future recommendations could be formulated to use valsartan as it would be more cost-effective, and side effects like dry cough could be avoided.

We found that, of the 204 cases (102 in each group), 42.16% (n=43) in Group A and 45.10% (n=46) in Group B were between the ages of 35 and 50, while 57.84% (n=59) in Group A and 54.90% (n=56) in Group B were between the ages of 51 and 70. The mean+sd was 51.06+8.42 in Group A and 50.73+8.06 years in Group B. Of these, 68.63% (n=70) in Group A and 64.71% (n=66) were male, while 31.37% (n=32) in Group A and 35.29% (n=36) were female. When valsartan and enalapril are compared for their ability to reduce proteinuria in patients with diabetic nephropathy, Group A experienced 37.25% (n=38) and 28.43% (n=29) efficacy, whereas Group B experienced 62.75% (n=64) and 71.57% (n=73) ineffectiveness; the p-value was 0.17.

Enalapril and losartan by themselves were found to reduce proteinuria by 33% ($p < 0.05$).[7] Another study shows the mean percentage reduction in proteinuria was 25.68 ± 21.40 with enalapril.[13] while the mean percentage reduction in proteinuria with valsartan is 33% (27-38%) (33 ± 21.4)[14].

Some studies show equal efficacy of enalapril and valsartan in reducing proteinuria, i.e, 33%.[15,16] While others show comparatively less efficacy of enalapril in reducing proteinuria, i.e, 25%.[17] Our findings are in agreement with this study reveals that enalapril had a lower rate of efficacy; however, the difference was not statistically significant.

Giancarlo Viberti and associates report that 332 individuals with microalbuminuria and DM-II, with or without High blood pressure, were assigned randomly to receive 80 mg/d valsartan or 5 mg/d amlodipine for 24 weeks. A blood pressure target of 135/85 mmHg was achieved by doubling the dose,

with doxazosin and bendrofluazide added as necessary. The outcome measure, primarily, was the percentage change in UAER (urine albumin excretion) between baseline and 24 weeks. There was a highly significant between-group effect (P<0.001) at 24 weeks, with the UAER being 56% (95% CI, 49.6 to 63.0) of baseline with valsartan and 92% (95% CI, 81.7 to 103.7) of baseline with amlodipine. In both the hypertensive and normotensive groups, valsartan comparably reduced UAER. When taking valsartan, more people saw a return to normoalbuminuria (29.9% versus 14.5%; P=0.001). In whole of the whole study period, the two treatments' BP reductions were similar (valsartan's systolic/diastolic was 11.2/6.6 mm Hg, amlodipine's was 11.6/6.5 mm Hg), and there was never a statistically significant difference between the groups in blood pressure readings in the normotensive or hypertensive subgroups.

They found that in individuals with DM-II and microalbuminuria, including the subgroup with baseline normotension, valsartan reduced UAER more efficiently than amlodipine at the same level of achieved BP and the same degree of BP decrease. This suggests that valsartan has an antiproteinuric action that is independent of blood pressure. Enalapril and losartan by themselves were found to reduce proteinuria by 33% ($p < 0.05$).[18]

However, considering the cost-effectiveness of Valsartan, we are of the view that this drug may be used, while enalapril has no significantly higher efficacy. The results of this study prove our hypothesis that "there is no difference in the efficacy of two drugs in lowering proteinuria among patients of diabetic nephropathy". Our results are required to be validated through some other multicentre studies.

CONCLUSION

We concluded that the efficacy of valsartan and enalapril in lowering proteinuria in patients with diabetic nephropathy is equal, and no significant difference is found; however, our results require validation through other multicentre studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Awais Asghar:** Conception of idea, data collection.
2	**Naila Unbreen:** Manuscript writing.
3	**Muhammad Owais Fazal:** Data analysis.
4	**Ghulam Abbas Tahir:** Data collection.
5	**Muhammad Usman Musharraf:** Results.